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VIRULENT SMALLPOX.

During the week ended June 26 two deaths from smallpox were reported in El Paso, Tex., and two cases of the disease with one death in the city of New Orleans, La.

During the week ended July 10 no new cases of smallpox were reported at New Bedford, Mass. The epidemic at this place seems to be under complete control.

POST-VACCINATION TETANUS.

STUDIES ON ITS RELATION TO VACCINE VIRUS.

By JOHN F. ANDERSON, Director, Hygienic Laboratory, United States Public Health Service.

Since 1902 the United States Public Health Service has, under authority of an act of Congress, exercised supervision over the manufacture and interstate sale of biological products such as vaccine virus, diphtheria antitoxin, etc. In this supervision the service has considered as coming under its jurisdiction the investigation of certain accidents which, on rare occasions, may follow the use of biologic products, such as the various manifestations of the serum disease or anaphylaxis, severe reactions after the use of bacterial vaccines, and the rare cases of tetanus occurring subsequent to vaccination with vaccinia.

Since 1904 the writer has paid particular attention to cases of tetanus following vaccination and has endeavored to collect accurate data concerning such accidents. These data have consisted, in part, of information in regard to the date of vaccination; result and character; date of onset of symptoms of tetanus; result; whether a shield was used; name of manufacturer of the virus used; samples of the same lot of virus; record of tests made by the manufacturer; number of doses of vaccine of the same lot of virus; and the number of persons vaccinated at the same time. Where it has been possible to secure samples of the same lot of virus used to vaccinate the person later developing tetanus, the virus has been exhaustively examined

in the Hygienic Laboratory for the presence of the tetanus organism and its toxin.

A number of the cases have either been investigated by the writer or by some other representative of the Public Health Service; for data in regard to the remaining cases the information was obtained, as a rule, through the local health officials.

In addition to the data on cases of tetanus following vaccination, there have been collected facts bearing on the number of vaccinations performed in the United States Army and Navy and the prevalence of tetanus among soldiers and sailors during the same period. As will be seen later, the latter data are of especial significance with regard to the theory put forth, by persons opposed to vaccination, who allege that tetanus germs sometimes are present in vaccine virus.

In order that the statistical and clinical data, as well as the laboratory findings, should have an experimental basis, a considerable number of experiments have been made upon animals in the laboratory with reference to the probability of infection with tetanus when animals susceptible to both vaccinia and tetanus were vaccinated with virus known to contain tetanus organisms, i. e., when the germs had been purposely placed therein for experimental reasons. The experimental results will be presented first.

It is known that the rhesus monkey is quite susceptible to vaccinia and also to tetanus. Therefore, to test the possibility of infecting this animal with tetanus through vaccination with virus heavily contaminated with tetanus spores, eight monkeys were vaccinated by multiple vaccinations with such virus.[1] All developed good "takes," which ran the usual course of a successful vaccination. None showed any evidence of infection with tetanus, although the presence of tetanus organisms was shown by examinations made of the crust or scab.

The guinea pig is acutely susceptible to tetanus and is also susceptible to vaccinia. With this fact in mind, a number of these animals were vaccinated with virus artificially heavily contaminated with the tetanus organism. Many of them developed good "takes," but none showed evidence of infection with tetanus.

It would appear from these animal experiments that, though the virus used for vaccination contained a large number of tetanus organisms, the bacilli failed to produce tetanus; nor was there absorption of sufficient tetanus toxin from the vaccination wound to produce symptoms of tetanus.

During the last 13 years there has been examined in the hygienic laboratory, specifically for the presence of the organism of tetanus, virus sufficient for the vaccination of over 2,000,000 persons, and in no

[1] Francis, Edward: Laboratory studies on tetanus. Hyg. Lab. Bull. 95, Washington, Govt. print. off., 1914.

instance were we able to show the presence of the tetanus germ or its products. The virus examined included samples of the same laboratory number (i. e., the same lot), and in several instances virus from the same package, as that used for the vaccination of persons who subsequently developed tetanus. It is certainly not unreasonable to assume that, had the virus contained tetanus bacilli, the organism would not have escaped detection in the laboratory, especially in view of the thorough mixing of the virus before it is dispensed by the maker.

This is of special significance when we consider that the methods for the detection of tetanus organisms have been so refined in the Hygienic Laboratory that we are able in practically all cases by a combination of tests to show their presence when known to be therein.[1]

It appears, therefore, proper to conclude that the virus so examined did not contain the tetanus organism. And it appears allowable to make the deduction that other portions of the same laboratory number of virus used for the vaccination of persons subsequently developing tetanus also did not contain the germ of tetanus.

An effort was made to ascertain the number of individual doses of vaccine sold by each licensed manufacturer during the 10-year period from 1904–1913, inclusive, and it was found that during that time there were sold for use in the United States approximately 40,000,000 individual doses of vaccine virus, and of this number 31,942,000 were not returned to the manufacturers, but were presumably used for vaccination. If the vaccine virus were the source of infection in persons developing tetanus subsequent to vaccination we should expect to find a considerable number of such cases, but I have been able to obtain information of only 41 authenticated cases. When we consider the small number of cases of tetanus and the large number (over 31,000,000) who were vaccinated, we are forced to the conclusion that the infection was not in the virus as sold and used in the United States, but was received in some other way than through the vaccine virus.

In addition, data of a similar kind, but with more direct bearing upon cases of tetanus following vaccination, were obtained.

Five cases of tetanus following vaccination were reported within a certain period and an effort was made to find out how many vaccinations were performed in the same State during the period in which these cases occurred. This was done by inquiring as to how many doses of virus were sent into that region, but figures were obtainable from but one distributor, although cases of tetanus had occurred among persons vaccinated with other virus. It was found that 71,796 vaccines had been sold in that State by one maker alone and

[1] Francis, Edward: Laboratory studies on tetanus. Hyg. Lab. Bull. 95, Washington, Govt. print. off., 1914.

probably as much or more by others. Moreover, this particular manufacturer had sold during the same period, for use in that State and elsewhere, over 209,000 vaccines; yet no other case of tetanus was reported among the users of that virus.

These five cases were closely studied, and we were fortunate, in several instances, to get the remaining virus from the package used for the patient or to get the laboratory number, and in this way to examine the laboratory records of the maker in which were set forth the results of the tests of the virus made before shipment. The records showed no evidence of tetanus in the virus examined. The tests of the virus from the same package likewise failed to reveal the presence of tetanus organisms therein. A study of these five cases showed the average incubation period to be 24 days, if counted from the date of vaccination.

These various data make it unreasonable to believe that the tetanus in this group of cases was due to the presence of tetanus spores in the virus used, and they support the supposition that the infection with tetanus was received otherwise than through the vaccine virus.

Another line of inquiry was in regard to the number of persons vaccinated in the United States Army and Navy [1] and the number of those so vaccinated who developed tetanus. It was believed that such information would be of particular value on account of the large number vaccinated and the completeness of the records. It was found that from 1904 to 1913, inclusive, 359,809 vaccinations were made in the Army and 225,028 in the Navy. In those 11 years, six cases of tetanus occurred in the Army, in none of which was there any reason to believe that vaccination had anything to do with the infection. For the same period there were but two cases in the Navy, neither of which bore any relation to vaccination, one case being subsequent to a railroad injury and the other being the result of an infected wound.

It certainly would seem that among this large number of vaccinations, a total of about 585,000, there would have occurred cases of tetanus had the virus prepared and sold in the United States been at fault. This is the more significant, as the virus used in the Army and the Navy is from the same sources as that generally used throughout the country.

The absence of tetanus following vaccination of 585,000 persons in the Army and the Navy is strong evidence in support of the opinion that the reported cases of tetanus following vaccination in the country at large during the period in question were due to infection received in a manner other than through the vaccine virus.

[1] I am indebted to the office of the Surgeon General United States Army and the Bureau of Medicine and Surgery, United States Navy, for this information.

We now come to the reported cases of tetanus which I have investigated since 1904. As few of the cases of tetanus following vaccination were reported in the medical press, use was made of press clippings to trace such cases. Whenever it was claimed that a case of tetanus was in any way connected with vaccination an effort was made to investigate it thoroughly. A total of 41 cases were studied and fairly satisfactory data were obtained covering most of them. A number of additional cases reported as tetanus were found upon investigation not to be tetanus, or were cases of tetanus clearly attributable to infection through injuries or wounds other than vaccination.

In many of the cases studied it was found that other persons had been vaccinated with the same lot of virus at the same time and, with a single exception, no other person suffered any ill effect. It was also found that many thousands of vaccines of the same lot of virus were used in other places and no case of tetanus followed their use. In a number of instances samples of the same laboratory number, or even from the same package, as that used for the vaccination of the person developing tetanus were obtained and examined in the Hygienic Laboratory for tetanus; but in no instance were we able to demonstrate the presence of tetanus organisms or toxin in the vaccine virus.

The records of tests of the virus, made by the manufacturers before placing the product on the market, indicated in every instance where it was possible to trace the lot an entire absence of any suggestion of tetanus in the virus, as shown by careful culturing and subcutaneous inoculations in animals. In several instances it was found that shields, usually of celluloid, had been used or that the vaccination wound had been neglected or had been exposed to infection in various ways. The average incubation period, if counted from the time of vaccination to the onset of tetanus, of the 41 cases would be 22 days.

Twenty-nine of the cases were fatal and 12 recovered, thus giving a case mortality of 70.7 per cent for the series. It is interesting to compare these figures with Willson's 52 cases of tetanus following vaccination, in which he found a case mortality of 78.8 per cent.[1] The average incubation period of his 42 cases in which the time was stated, counting from date of vaccination to onset of tetanus, was 19.4 days. The combined figures for the two series are given in the following table:

Series.	Number of cases.	Number died.	Number recovered.	Percentage of mortality.
Willson	52	41	11	78.8
Anderson	41	29	12	70.7
Total	93	70	23	75.2

[1] Willson, Robert N.: An analysis of 52 cases of tetanus following vaccinia. With reference to the source of infection. 1839-1902. J. Am. M. Ass., 1902, vol. 38, pp. 1147, 1222.

The average of the suppositious incubation periods, counting from the time of vaccination to the onset of tetanus, in the combined series of 83 cases was 20.7 days.[1]

In this connection it is significant to compare the mortality of tetanus due to other causes with regard to the period of incubation and the mortality of the cases following vaccination. It is a well-known observation that the mortality of cases of tetanus with an incubation period of less than 10 days is much higher than that of cases with a longer incubation period. In the series of 858 cases of tetanus reported by Anders and Morgan,[2] 588 were found to have an incubation period of 10 days or less, and of this number 363 were fatal, or a mortality of 61.7 per cent. There were 270 with an incubation of more than 10 days, 112 of which were fatal, showing a mortality of 41.5 per cent.

It will be recalled that the average mortality for the combined series of Willson's and the writer's cases of tetanus following vaccination, 93 in number, was 75.2 per cent. According to the statistics of mortality from tetanus, this corresponds with or is higher than the mortality from cases having an incubation period of 10 days or less. The incubation period of our combined series was 20.7 days, if counted from the date of vaccination.

Now, what is the significance of these figures? We find that in tetanus following vaccination the average period from vaccination to onset of symptoms is 20.7 days, while the average mortality is 75.2 per cent, this high mortality rate being similar to that in cases of tetanus with an incubation period of 10 days or less.

It appears evident from this that the infection was received 10 days or more after vaccination, and therefore was probably not received through the virus used for vaccination. Many of the cases following vaccination give a history of having the vaccination scab or crust removed in some way, thus permitting infection of the wound, with a re-formation of the crust and the establishment of anaërobic conditions. It is to be noted that the scab begins to form about the tenth day or later.

From a consideration of the foregoing the following summary seems permitted:

1. That it is difficult, if not impossible, to produce tetanus in susceptible animals by vaccination with virus containing large numbers of tetanus organisms which have been purposely placed therein.

2. That, in view of the failure to demonstrate tetanus organisms in the large amount of vaccine virus specifically examined for that purpose, it seems exceedingly improbable that vaccine virus as sold in the United States contains tetanus organisms.

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[1] The incubation period in Willson's series was given in only 42 of the 52 cases.

[2] Anders, James M., and Morgan, Arthur C.: Tetanus: A preliminary report of a statistical study. J. Am. M. Ass., 1905, vol. 45, p. 314.

3. That from 1904 to 1913, inclusive, over 31,000,000 doses of vaccine virus were used in the United States, yet information was obtained of only 41 authenticated cases of tetanus occurring subsequent to vaccination. From this it is concluded that had the vaccine virus used during that time in the United States been at fault many more cases of tetanus should have followed vaccination.

4. That in view of the large number of vaccinations (about 585,000) done in the United States Army and Navy and the absence from them of a single case of tetanus following vaccination, the cases of tetanus following vaccination in the country at large were not due to infection contained in the virus.

5. That the average period from vaccination to onset of symptoms of tetanus in 83 cases of tetanus following vaccination was 20.7 days, while the average mortality of 93 cases was 75.2 per cent, this being slightly higher than the mortality of cases of tetanus due to other causes with an incubation period of 10 days or less.

Conclusions.

Cases of tetanus occurring 15 or 20 days subsequent to vaccination do not receive their infection through the vaccine virus, but in all probability the infection is received about the tenth day or later after vaccination.

The infection with tetanus is received by a contamination of the vaccination wound, such as may occur in the infection of any other surgical wound not properly cared for.

ANOPHELES AS A WINTER CARRIER OF PLASMODIUM.

THE MOSQUITO AS A PROPHYLACTIC INDICATOR.

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This study was conducted during the period between February 3 and June 1, 1915. For the purpose a locality was selected proven to have had a malarial index of 40.9 per cent during September, 1914. At this time a total of 1,666 persons were examined.

A field laboratory was established at Scott, Miss., on the property of the Mississippi Delta Planting Co., a syndicate of planters controlling 15 contiguous plantations in Bolivar and Washington Counties. Acknowledgment is made of the intelligent cooperation of Drs. Miller and Lane, of Scott, and Mr. Salsbury and Prof. Fox, of the Mississippi Delta Planting Co., who lent every facility in their power for the pursuit of this investigation.

Material for the study was obtained in and about habitations and in the woods and swamps. House and stable inspections upon the various plantations were instituted in an effort to collect resting mosquitoes, but this soon proved not to be a fruitful source. Not